

DOCKET NO.: DAVI-0005
 Application No.: 09/787,082
 Office Action Dated: September 9, 2004

Amendments to the Specification:

Please amend the table on page 8, lines 1-34 as follows:

Conotoxin	Sequence
Omega conotoxins	
MVIIA	CKGKGAKCSRLMYDCCTGSCRS -- GKC (SEQ ID NO:10)
MVIIC	CKGKGAO CRKTMYDCCSGSCGRR -- GKC (SEQ ID NO:11)
GVIA	CKSOGSSCSOTSYNCCR – SCNOYTKRCY (SEQ ID NO:12)
SVIA	CRSSGSOCGVTSI – CCGR – CYR -- GKCT (SEQ ID NO:13)
SVIB	CKLKGQSCRKTSYDCCSGSCGRS – GKC (SEQ ID NO:14)
GVIIA	CKSOGTOCSRGM RDCCTS – CLLYSNKCRRY (SEQ ID NO:15)
GVII B	CKSOGTOCSRGM RDCCTS – CLSYSNKCRRY (SEQ ID NO:16)
TVIA	CLSOGSSCSOTSYNCCRS – CNOYSRKCR (SEQ ID NO:17)

Kappa conotoxin

PVIIA CRIONQKCFQHLDCCSRKCNRFNKC V (SEQ ID NO:18)

Alpha conotoxins

GI ECCNPA – CGRHYS -- C (SEQ ID NO:19)
 IMI GCCSDPRCAWR ---- C (SEQ ID NO:20)
 PNIA GCCSLPPCAANNPDYC (SEQ ID NO:21)
 PNIB GCCSLPPCALS NPDYC (SEQ ID NO:22)
 SII GCCCN PACGP NYG -- CGTSCS (SEQ ID NO:23)
 MII GCCSNPBCHLEHSNLC (SEQ ID NO:24)

Mu conotoxin

GIIIA -RDCCTOOKKCKDRQCKOQRCCA (SEQ ID NO:25)
 GIIB -RDCCTOORKCKDRRCKOMKCCA (SEQ ID NO:26)
 GIIC -RDCCTOOKKCKDRRCKOLKCCA (SEQ ID NO:27)

PIIIA ZRLCCGFOKSCRSRQCKOHRCC (SEQ ID NO:28)

GS ACSGRGSRCPPQCCMGLRCGRGNPQKCIGAHEDV (SEQ ID NO:29)

Please amend the paragraph beginning on page 21, line 9-17 as follows:

The residues in bold represent the sequence of MVIIA. Those not in bold are the linking moiety (TRNGLPG SEQ ID NO.: 1). A thioester method has been used in the synthesis of this peptide which was performed on a Gly PAM resin. A -SCH₂-CH₂CO-linker was attached to the Gly-PAM resin by treating the resin with bromopropanoic acid for 30 minutes, washing with DMF and then treating the resin with 10 % thioacetic acid, 10 % DIEA in DMF for 2 x 20 minutes. The resin was again washed with DMF and treated with 10 % β-mercaptoethanol, 10% DIEA in DMF for 2 x 20 minutes. After a final wash with DMF, the first residue, Boc-glycine, was coupled to the resin using HBTU and DIEA. The remainder of the peptide was assembled by manual synthesis using HBTU with *in situ* neutralization (Schnölzer, M. *et al.*, 1992).

Please amend the paragraph beginning on page 22, line 8-14 as follows:

Once again the bold residues correspond to the sequence of MVIA, (all except TRNG SEQ ID NO:2). This peptide was synthesised using the procedures outlined in Example 1. Following cyclisation, cyclo-MVIIA 2 was oxidised at a concentration of 0.5 mg/mL in 2 M (NH₄)₂SO₄, 0.1 M NH₄OAc (pH 8) and 1 mM reduced glutathione at 4 °C for 24 hours. Three major components were present in the oxidation and were all purified using a semi-preparative C18 column (3mL/min) with monitoring at 230 nm. The three components represent cyclic fully disulfide bonded forms of cyclo-MVIIA-2.

Please amend the paragraph beginning on page 25, line 19-26 as follows:

The peptide has both an N(~~GLPU~~) N(GLPV) and C(TRG) terminal extension and the remaining residues (in bold) represent MVIIA. The reduced peptide was purified using the conditions given in Examples 1 and 2. Oxidation was achieved using 0.1 M ammonium acetate, 2M ammonium sulfate, pH 7.7, 1mM reduced glutathione and the reaction left at 4 °C for two days. The oxidised peptide was purified and the activity tested as in Example 3. An EC₅₀ of 1.081×10^{-9} M was found for this analogue, illustrating that extending the N and C termini of the peptide, as may be necessary prior to cyclisation, does not eliminate activity.

Please amend the paragraph beginning on page 26, line 1-6 as follows:

A cyclic α -conotoxin is prepared based on the sequence of α -conotoxin MII. The linear precursor for this synthesis is designed by first adding a linker moiety to the native sequence as shown below. The residues in bold correspond to the native sequence of MII and the non-bold residues are the linker moiety (TNG SEQ ID NO: 4).